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ASBMT
American Society for Blood and Marrow Transplantation

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Update of the 2006 Evidence-Based Review

Among the primary objectives of the American Society for Blood and Marrow Transplantation (ASBMT) are to:

- Define commonly accepted medical and evidence-based practice
- Develop standards of medical care for autologous and allogeneic transplants
- Provide recommendations for physicians, patients, and third-party payers on the role of transplantation as a therapeutic approach.

Toward this end, in 1999 the Society began sponsoring evidence-based reviews (EBRs) of the scientific and medical literature to document when blood and marrow transplantation is indicated in the treatment of selected diseases.

In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly, at approximately 5-year intervals. The adult acute lymphoblastic leukemia (ALL) EBR is the second in the series to be updated.

GOALS

The goals of the EBRs are to:

- Assemble and critically evaluate all valid, peer-reviewed evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) related to the disease
- Provide treatment recommendations based on the available evidence
- Identify discrepancies in study design or methodology among published studies that may impact the quality of the evidence
- Identify areas of needed research.

The goals of the Adult ALL EBR update are to:

- Provide a summary of recent clinical evidence
- Provide timely treatment recommendations
- Determine if new evidence strengthens or changes treatment recommendations provided in the original Adult ALL EBR published in 2006.

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UPDATED TREATMENT RECOMMENDATIONS FOR ADULT ALL

The following updated treatment recommendations are offered for the role of SCT as treatment for ALL in adults, and are based on consensus reached by an expert panel[1] following a systematic review of the literature [1] published since the 2006 original EBR [2].

Autologous SCT versus non-transplantation Therapy for ALL in First Complete Remission (CR1)

- New evidence indicates that in the absence of a suitable allogeneic donor, autologous SCT may be an appropriate therapy because of similar survival outcomes and a shorter treatment duration when compared with chemotherapy alone, but results in a high relapse rate. Maintenance therapy, biologic therapy, or tyrosine kinase inhibitors may improve outcomes in selected patients, but these approaches need further study.

Allogeneic SCT versus non-transplantation Therapy for ALL in CR1

- New data indicate that myeloablative allogeneic SCT is an appropriate treatment for adult ALL in CR1 for all disease risk groups. Allogeneic SCT provides a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. In older (>35 years), standard risk, Ph-negative ALL patients, a higher transplant-related motality diminishes the significant survival advantage with allogeneic SCT.

Allogeneic SCT versus non-transplantation for ALL in ≥CR2

- New data confirm the original treatment recommendation favoring allogeneic SCT over chemotherapy for ALL in CR2 or greater.

Autologous versus Allogeneic SCT

- New data strengthen the original treatment recommendation favoring allogeneic over autologous SCT. There are insufficient data to determine if this effect is more apparent in disease risk subgroups, including Ph+ ALL.

Related versus Unrelated Donor Allogeneic SCT

- New data confirm the original recommendation that there are similar, and possibly equivalent, survival outcomes after related and unrelated allogeneic SCT. Post-SCT complications may differ.

Unrelated Donor Cord Blood Transplant versus Unrelated Donor BMT

- New data indicate it is appropriate to consider cord blood transplantation for patients with no HLA-well-matched donor option or those needing an urgent transplant.

Imatinib versus No Imatinib Pre- and/or Post-SCT in Ph-Positive ALL

- New data suggest imatinib therapy before and/or after SCT yields significantly superior outcomes in overall survival and leukemia-free survival. Ongoing studies using other tyrosine kinase inhibitors may strengthen this recommendation.

Comparison of Induction Therapies before SCT

- New data were insufficient to make a treatment recommendation regarding the benefit of any 1 induction regimen.

Allogeneic SCT: Conditioning

- There are not enough data to make a recommendation of the superiority of any 1 conditioning regimen. As in the original recommendation, there appears to be a benefit to total body irradiation-containing regimens compared with non–total body irradiation-containing regimens.
- New data suggest reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but are insufficient to make a recommendation on the use of reduced-intensity conditioning. Thus, reduced-intensity regimens are appropriate only for adult patients with ALL in remission who are unsuited for myeloablative conditioning.

AREAS OF NEEDED RESEARCH

After reviewing the updated evidence, the expert panel identified the following important areas of needed research in adult ALL:

1. re-evaluate allogeneic SCT versus more intensive chemotherapy regimens, especially in younger (<35 years) adults, and in the context of biologic therapies and tyrosine kinase inhibitors (for Ph+ ALL).
2. Assess the ability of tyrosine kinase inhibitors to reduce the leukemia burden pre- or post-SCT in Ph+ ALL patients and evaluate whether this can improve survival outcomes after autologous and allogeneic SCT. Studies of different tyrosine kinase inhibitors, doses, and schedules will be important.
3. Improvement in the detection and monitoring of minimal residual disease during initial treatment to guide individual patient eligibility and timing of allogeneic SCT.
4. Monitoring of minimal residual disease after SCT to detect early post-SCT relapse in need of preemptive therapy. This may indicate patients at higher risk of early recurrence, but effective therapy will also need to be developed.
5. Indications for using reduced-intensity versus myeloablative conditioning regimens for allogeneic SCT. The broad range of conditioning intensity will need further study, adjusted for a patient's tolerance of conditioning toxicity balanced against the risk of relapse.
6. Evaluation of cord blood transplantation techniques, such as single unit, double unit, and *ex vivo* expansion, to improve survival outcomes and reduce transplant-related mortality. Larger multicenter experience will be needed to more fully evaluate the broader applicability of cord blood grafting for adults with ALL.
7. Assessment of patient quality of life and functional status after successful SCT.
8. Assess the impact of management plans and follow-up care to facilitate better quality of life for ALL patients, regardless of treatment.

REFERENCES

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